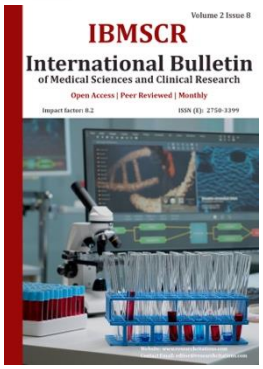


# ROLE OF ENDOTHELIAL DYSFUNCTION IN THE DEVELOPMENT OF ISCHEMIC STROKE

**Sh.B.Usmonova**

https://doi.org/10.5281/zenodo.14062049

**ABSTRACT**

Cerebrovascular disease, particularly ischemic stroke, is indeed a significant global health concern. It has become one of the leading causes of disability and the second leading cause of death worldwide. Ischemic stroke, which accounts for approximately 85% of all strokes, occurs when a blood clot or other obstruction restricts blood flow to the brain, leading to a lack of oxygen and nutrients that can cause brain damage. Understanding its risk factors is crucial for prevention and targeted treatment. The endothelium plays a crucial role in maintaining vascular homeostasis, primarily through its ability to regulate the processes of vasodilation (widening of blood vessels) and vasoconstriction (narrowing of blood vessels). It achieves this by producing and releasing cytokines and various chemical mediators. There are many factors which can induce Endothelialdysfunction. Hyperhomocysteinemia is considered one of these factors.

**Key words**: Ishemic stroke, homocystein, endothelial dysfunction, hyperhomocysteinemia

**АННОТАЦИЯ**

Цереброваскулярные заболевания, особенно ишемический инсульт, представляют собой серьёзную глобальную проблему здравоохранения. Ишемический инсульт, на который приходится около 85% всех инсультов, является одной из ведущих причин инвалидности и второй по значимости причиной смерти во всем мире. Этот тип инсульта происходит, когда кровяной сгусток или другая преграда блокируют кровоток к мозгу, вызывая дефицит кислорода и питательных веществ, что может привести к повреждению мозга. Понимание факторов риска крайне важно для профилактики и целенаправленного лечения. Эндотелий играет ключевую роль в поддержании сосудистого гомеостаза, главным образом за счёт способности регулировать процессы вазодилатации (расширения сосудов) и вазоконстрикции (сужения сосудов), что достигается производством и выделением цитокинов и различных химических медиаторов. Существует множество факторов, которые могут вызвать эндотелиальную дисфункцию, и гипергомоцистеинемия считается одним из таких факторов.

**Ключевые слова**: ишемический инсульт, гомоцистеин, эндотелиальная дисфункция, гипергомоцистеинемия.

**ANNOTATSIYA**

Serebrovaskulyar kasalliklar, ayniqsa ishemik insult, jahon sog'liqni saqlash sohasidagi dolzarb muammolardan biridir. Ishemik insult barcha insultlarning taxminan 85% ni tashkil etadi va dunyoda nogironlikning asosiy sabablaridan biri hamda o'lim bo'yicha ikkinchi o'rindagi sabab hisoblanadi. Bu turdagi insult qon tomir trombi yoki boshqa to'siq miyaning

qon bilan ta'minlanishini cheklaganda yuzaga keladi va kislorod hamda oziq moddalar yetishmasligi tufayli miya hujayralariga zarar yetkazadi. Ushbu kasallik xavf omillarini aniqlash, uning oldini olish va maqsadli davolash uchun juda muhimdir. Endoteliy qon tomir gomeostazini saqlashda muhim rol o'ynaydi va asosan tomirlarning kengayishi (vazodilatatsiya) va torayishini (vazokonstriksiya) boshqarish orqali amalga oshiriladi. Buning uchun endoteliy sitokinlar va boshqa kimyoviy moddalarning ishlab chiqarilishi va chiqarilishini ta'minlaydi. Endotelial disfunktsiyani keltirib chiqaradigan ko'plab omillar mavjud, va giperhomosisteinemiya ushbu omillardan biri sifatida qabul qilinadi.

**Kalit so'zlar**: ishemik insult, gomosistein, endotelial disfunktsiya, gipergomosisteinemiya.

**Introduction**

Acute ischemic stroke (AIS) is one of the most common cerebrovascular diseases which accompanied by a disruption of aminothiols homeostasis(1). The comprehension that elevated homocysteine (Hcy) in plasma might predispose to arterial or venous thromboembolism emerged more than 40 years ago, when patients with homocysteinuria were observed to have a high risk of early vascular disease(2).Elevated tHcy is known to increase oxidative stress, diminish vasodilation, stimulate the proliferation of vascular smooth muscle cells, alter the elastic properties of the vascular wall and thus increase the risk for atherosclerosis. Atherosclerosis caused by hypertension is the most important risk factor for IS and CHD . found that the odds ratios of vascular disease in male, were 2.2 for the highest quartiles (versus remainder) of tHcy, 3.9 for hypertension, and over 10.0 for both. (3)

The review article is aimed to conduct a meta-analysis of published studies to investigate the relationship between plasma homocysteine (Hcy) levels and the risk of ischemic stroke.

**Purpose of the study.** This article examines and summarizes published studies on relationship between hyperhomocysteinemia and ischemic stroke to identify whether hyperhomocysteinemia could become a risk factor for ischemic stroke .

**Materials and methods.** Performing a systematic literature search for scients study works and articles written during last ten years about connection between hyperhomocysteinemia and ischemic stroke from Pubmed and Google scholar bases.

**Main part.**Cerebrovascular disease, particularly ischemic stroke, is indeed a significant global health concern. It has become one of the leading causes of disability and the second leading cause of death worldwide. Ischemic stroke, which accounts for approximately 85% of all strokes, occurs when a blood clot or other obstruction restricts blood flow to the brain, leading to a lack of oxygen and nutrients that can cause brain damage(4).

During the past year epidemiological studies have linked elevated plasma total homocysteine concentrations with an increased risk of ischaemic stroke because of arterial disease. Laboratory studies have further explored the mitogenic effects of total homocysteine on vascular smooth muscle, and cytotoxic and thrombophilic effects on vascular endothelium(5).

Homocysteine (Hct) is a toxic amino acid, formed as a demethylated by-product of methionine. It is typically eliminated through a remethylation process involving methionine synthase, which uses methylcobalamin as a co-factor and 5-methyl tetrahydrofolate as a methyl donor. In the brain, Hct is primarily broken down by being remethylated back to methionine, relying on methylcobalamin and folate(6).

Since B vitamins (B6, B12, and folate) are essential co-factors in this catabolic process, elevated levels of homocysteine (iHct) can indicate a deficiency in these vitamins. The Hct-methionine cycle plays a crucial role in producing S-adenosylmethionine (SAM), a key methyl donor for various biological reactions(6) .

Excessive Hct is associated with damage to major brain blood vessels, either by disrupting the methylation balance (SAM/SAH ratio) or through direct effects, potentially leading to ischemic stroke(7).

Chinise researchers named Chongke Zhong, Liying Lv, Changjiang Liu, Liang Zhao, Mo Zhou, Wenjie Sun, Tan Xu, Weijun Tong recruited a total of 3695 acute ischemic stroke patients from three hospitals in northern Chinese cities between June 1, 2009 and May 31, 2013. Demographic characteristics, lifestyle risk factors, medical history, and other clinical characteristics were recorded for all subjects. They defined poor outcome as a discharge modified Rankin Scale (mRS) score ≥3 or death. They used multivariate non-conditional logistic regression models to analyze association between homocysteine concentration, admission blood pressure, and risk of poor outcome following acute ischemic stroke.

They got a result that Those in the highest quartile of Hcy concentration had a significantly increased risk of poor outcomes after an ischemic stroke, with an odds ratio (OR) of 1.33, indicating a 33% higher risk compared to the lowest quartile.As well as ,They found that there was a dose-response relationship between Hcy levels and poor outcomes , with a significant trend ($p = 0.027$).They revealed that high BP alone was also significantly associated with poor outcomes, with an adjusted OR of 1.44, suggesting a 44% increased risk.(8)

The case-control study which was carried out by Nahid Ashjazadeh, MD, Morteza Fathi, MD, and Abdohamid Shariat, MD described that 171 ischemic stroke patients and 86 controls were analyzed for factors including fasting total homocysteine (tHcy), vitamin B12, and folate levels to assess the relationship between elevated tHcy levels and stroke subtypes, particularly cardioembolic strokes, using the TOAST classification. According to this study, the mean fasting Hcy level was higher in stroke patients (16.2 µmol/L) compared to controls (13.5 µmol/L), with a P value of 0.013, indicating statistical significance. They also found that Hcy levels were particularly elevated in patients with cardioembolic strokes (17.7 µmol/L), with a P value of 0.010, showing a stronger association with this subtype. As well as, the odds of having ischemic stroke were significantly higher in individuals with tHcy levels above 15 µmol/L, with an adjusted odds ratio of 2.17 (P=0.004)(9).

Other researchers from China (Elevated total homocysteine levels in acute ischemic stroke are associated with long-term mortality Zhihong Shi, Yalin Guan, Ya Ruth Huo, Shuling Liu, Meilin Zhang, Hui Lu, Wei Yue, Jinhuan Wang, Yong Ji) conducted the study involved 3,799 patients admitted for acute ischemic stroke, with tHcy levels assessed within 24 hours of admission. Patients They followed patients for an average of 48 months.In the study, they found that out of the patients, 233 (6.1%) died during the follow-up and after adjusting for various risk factors (age, smoking, diabetes, etc.), patients in the highest tHcy quartile (>18.6 µmol/L) had a 1.61 times higher risk of death compared to those in the lowest quartile (≤10 µmol/L). The study showed that this relationship was only significant in patients with large-artery atherosclerosis (adjusted HR 1.80), but not in those with small-vessel occlusion. As well as,stroke-related deaths were 2.27 times higher in patients in the third tHcy quartile and

2.15 times higher in the fourth quartile compared to the lowest quartile. However, tHcy levels were not linked to cardiovascular mortality or recurrent ischemic stroke.(10)

Moreover,neurologists from Indonesia (Association of High Blood Homocysteine and Risk of Increased Severity of Ischemic Stroke Events Salim Harris et al. Int J Angiol. 2019 Mar) carried out the cross-sectional study from July 2017 to January 2018 to examine that hyperhomocysteinemia can affect stroke severety.Their study ncluded 77 patients with acute ischemic stroke, grouped by their homocysteine levels: low (<9 µmol/L), moderate (9-15 µmol/L), and high (>15 µmol/L). Their research showed a clear association between higher homocysteine levels and greater stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS). Patients with high homocysteine levels were found to be 14.4 times more likely to experience severe strokes (NIHSS > 5) compared to those with low levels, and 3.9 times more likely compared to those with moderate levels(11).

**Conclusion.** Elevated homocysteine levels have emerged as a significant, independent risk factor for ischemic stroke, with varying impacts depending on the stroke subtype. The studies above by Chongke Zhong et al.(2014) , Ashjazadeh et al. (2013) , Zhihong Shi et a.l (2015) and Int J Angiol. (2019 ) underscore the need for further research to delineate the mechanisms by which hyperhomocysteinemia influences stroke risk and to explore effective strategies for mitigating this risk. Given the modifiable nature of homocysteine levels, early detection and intervention may play a critical role in reducing the incidence of ischemic stroke, particularly in populations vulnerable to specific stroke subtypes such as cardioembolic or intracranial stenosis-related strokes

## References:

1. Impact of homocysteine on acute ischemic stroke severity: possible role of aminothiols redox status Wei-Chong Dong et al. BMC Neurol. 2024.
2. McCully KS. Atherogenesis and the chemical pathology of homocysteine. European Journal of Laboratory Medicine 1996; 4:121–128
3. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245
4. Bamford J, Sandercock P, Dennis M, et al. A prospective study of acute cerebrovascular disease in the community: the oxfordshire community stroke project 1981–86. (1 Methodology, demography and incident cases of first-ever stroke. J Neurol Neurosurg Psychiatry. (1988) 51:1373–80. 10.1136/jnnp.51.11.1373 [DOI] [PMC free article] [PubMed] [Google Scholar
5. Hankey GJ, Eikelboom JW. Homocysteine and stroke. Curr Opin Neurol. 2001 Feb;14(1):95-102. doi: 10.1097/00019052-200102000-00015. PMID: 11176224.
6. Wald NJ, Med D, Watt HC, Law MR, Weir DG, Mcpartlin J, et al. Homocysteine and Ischemic Heart Disease. Arch Intern Med. 2008;158: 862–867. [DOI] [PubMed] [Google Scholar]
7. Bots ML, Launer LJ, Lindemans J, Hoes AW, Hofman A, Witteman JCM, et al. Homocysteine and short-term risk of myocardial infarction and stroke in the elderly: The Rotterdam Study. Arch Intern Med. 1999;159: 38–44. doi: 10.1001/archinte.159.1.38 [DOI] [PubMed] [Google Scholar]
8. Zhong C, Lv L, Liu C, Zhao L, Zhou M, Sun W, Xu T, Tong W. High homocysteine and blood pressure related to poor outcome of acute ischemia stroke in Chinese population. PLoS One.

2014 Sep 29;9(9):e107498. doi: 10.1371/journal.pone.0107498. PMID: 25265507; PMCID: PMC4180067.

9. Ashjazadeh N, Fathi M, Shariat A. Evaluation of Homocysteine Level as a Risk Factor among Patients with Ischemic Stroke and Its Subtypes. Iran J Med Sci. 2013 Sep;38(3):233-9. PMID: 24174694; PMCID: PMC3808947.

10. Shi Z, Guan Y, Huo YR, Liu S, Zhang M, Lu H, Yue W, Wang J, Ji Y. Elevated Total Homocysteine Levels in Acute Ischemic Stroke Are Associated With Long-Term Mortality. Stroke. 2015 Sep;46(9):2419-25. doi: 10.1161/STROKEAHA.115.009136. Epub 2015 Jul 21. PMID: 26199315; PMCID: PMC4542568.

11. Harris S, Rasyid A, Kurniawan M, Mesiano T, Hidayat R. Association of High Blood Homocysteine and Risk of Increased Severity of Ischemic Stroke Events. Int J Angiol. 2019 Mar;28(1):34-38. doi: 10.1055/s-0038-1667141. Epub 2018 Jul 26. PMID: 30880891; PMCID: PMC6417904.